REMARKS

Claims 1-40, 53-61, 133-136, 173-176 and 178-186 are pending. Claims 1-8, 11, 13-19, 22-36, 38-40, 53-61, 133-136, 173-176 and 183-186 are rejected and the remaining claims are withdrawn. The Office also indicates that claims 31-32, 40 and 56 are withdrawn as drawn to a non-elected species.

Claims 1, 23, 136 and 185-186 are objected to for improper abbreviation, inconsistent nomenclature within the claims and typographical errors. Applicant has amended the claims herein and submits that these objections now should be withdrawn.

The Office has required that material referred to as incorporated by reference from the Mihelić et al. publication. Applicant has amended the specification herein as requested to add Table I. Mihelić contains a listing of the amino acid sequences of thymosin beta 4 peptides TB4, TB4ala, TB4xen, TB9, TB9 met, TB10, TB11, TB12, TB12perch, TB13 and TB14. The material being inserted in this amendment is the material incorporated by reference. This amendment contains no new matter. The spelling of the name "Mihelic" also has been corrected here to read "Mihelić."

Concerning the issue of priority, Applicant submits that the structure of thymosin beta 4 and its isoforms were well known to those of skill in the art at the time the priority provisional application was filed. The LKKTET motif also was well known at that time. Applicant therefore submits that the disclosure of thymosin beta 4 would lead the skilled artisan to this motif sequence and to isoforms as claimed in the claims presented here. Therefore the application is entitled to the priority date of the provisional application here.

The Office asserts that prior application PCT/US99/17282 lacks disclosure of lactated Ringer's intravenous polyalkylene glycol. However, this reference discloses intravenous administration (page 16, line 17), lactated Ringer's intravenous vehicles (page 16, line 25), and the addition of common excipients to formulations for parenteral

administration, including polyalkylene glycols (page 14, line 29 – page 15, line 1). This material is supported in the priority document and is entitled to its priority date.

The Office asserts that prior application PCT/US99/17282 lacks written description of "'about' 0.01 ng/ml or 'about' 60 µg per 300 microliters." The numerical amounts 0.01 ng/ml and 60 µg per 300 microliters are found in PCT/US99/17282 at page 33, line 11 and page 29, line 16, respectively. Applicant submits that the person of skill in the art would recognize that the inventors of the present invention possessed the invention in the range between these disclosed amounts since the working examples showed that both dosages were effective. Applicant submits that this disclosure therefore meets the standards of 35 U.S.C. § 112, first paragraph for written description. The word "about" has been deleted from the claims. Applicant therefore submits that claims 173-176 are entitled to priority at least to the prior PCT application.

The Office considers the language "neuron-degenerative disease" not to be supported in prior PCT application PCTUS99/17282. Applicant has deleted this language and now submits that these claims are entitled to priority at least to the filing date of this PCT application.

Claims 1-8, 11, 13, 22-30, 33-36, 38-39, 53, 61, 133-136, 173-176 and 183-186 are rejected as indefinite.

The Office refers to "isoforms," which assertedly are not identified, have no structural features or are incorporated by reference. The present specification, however, describes TB4 isoforms as having about 70%, 75% or 80% homology to the sequence of TB4 in Figure 10, and provides numerous examples at page 9, lines 23-24, with sequences provided in new Table I and Figure 11. The specification also describes the structural and functional features that these TB4 isoforms share. For example, the isoforms share an actin-binding motif, LKKTET (or a conservative variant thereof) and share the ability to polymerize, bind and/or sequester actin. The specification describes these features on pages 9-10 of the specification and specifically states that peptides having the ability to sequester actin, such as peptides that have the known actin-binding motif sequence LKKTET (and the numerous

specifically identified peptides that are well known to the artisan which are known to have an actin-binding sequence and an actin-binding function listed on page 10, lines 21-26 and the TB4 isoforms at page 10, line 10) are useful in the invention. Applicant submits that the structural feature of the isoforms as defined here is clear and correlated to the functional feature. The isoforms and other peptides useful in the invention contain a motif that imparts the function of actin-binding.

The disclosures in the specification here, which correlate structure and function, together with the general knowledge in the art, provide ample definition of the term isoform, as it is used in the claims here. To make this relationship clearer, Applicant has amended the claims to recite a TB4 isoform that comprises LKKTET (SEQ ID NO:1) or LKKTET (SEQ ID NO:1) in which a hydrophobic amino acid residue is replaced with another hydrophobic amino acid residue or a polar amino acid residue is replaced with another polar amino acid residue or both. Applicant submits that, given the knowledge of the skilled artisan and the discussion in the specification, the claim term is definite and clear, and apprises the reader of the intended scope.

The Office refers to the phrase "conservative variant" in claims 1, 23 and 185-186. This term has been deleted from the claims in rewriting. Applicant submits that this term is defined in the specification, however, and is clear. See page 11, lines 1-6. Applicant requests withdrawal of any rejection made on this basis.

Claims 1-8, 11, 13, 22-30, 33-36, 38-39, 53, 61, 133-136, 173-176 and 183-186 are rejected as lacking sufficient written description. The Office Action does not clearly state what features of these claims are not supported sufficiently, however the Action refers to a polypeptide or a conservative variant or isoform having wound-healing activity. Applicant is assuming that this feature is the basis for this rejection and requests clarification if this is not the case.

The Office considers the level of skill in the art to be "low" with respect to understanding functional effects of varying a peptide sequence. Applicant submits that this is not the case in the context of the present invention. The claims here refer to polypeptides, each of which contains the peptide sequence LKKTET (SEQ ID NO:1) or

this same sequence wherein a hydrophobic amino acid residue is replaced with another hydrophobic amino acid residue or a polar amino acid residue is replaced with another polar amino acid residue. The phrase "conservative variant" is not contained in the amended claims.

As disclosed in the specification as originally filed, and as is well known in the art, the twenty naturally-occurring amino acids commonly found in proteins have known structures, with side chains that are hydrophobic in some cases and polar in some cases. A substitution of the kind recited in the claim of an amino acid in the LKKTET sequence would not result in sequences that are so numerous or so varied that a skilled artisan would doubt that the inventors have possessed the invention. Given the large number of peptides which contain the LKKTET motif sequence or a close variant thereof and which possess the actin-binding function of these sequences, the skilled person, who would have been aware of this motif and its variants, and the retained actin-binding activity imparted by these sequences, would not have doubted the workability of the invention in the full scope as claimed here. Applicant has connected the structure and function of the claimed motifs and wound healing activity. Therefore, in summary, Applicant submits that the effects of varying the LKKTET motif sequence in the limited fashion of the present claims is well understood such that the effects of these substitutions can be predicted.

In discussing the issue of "partial structure," the Office concentrates on the portions of the peptide molecules that are not the motif. As disclosed in the specification, it is a particular motif that imparts function. Therefore, changes to other portions would have been understood not to have major effects on the function. The term "conservative variant," although specifically described in the application, no longer is used in the claims. The term "isoform" is one which is understood in the art. A skilled artisan would not consider all random variants of TB4 to necessarily be an "isoform" of TB4 and does not define the term "isoform" to include all mathematically possible variations of the sequence. Hence, this is not the broadest reasonable interpretation of the term as it would be understood by one of skill in the art.

An isoform of a peptide is understood by persons of skill to be a different form produced from a related gene or by alternative splicing of the same gene. Many of these related genes are known in the art and are disclosed and described in the present specification. The sequences of a number of isoforms are provided in the specification. Persons of skill recognize what these are, and should additional related genes be discovered in the future, would easily recognize these as part of the same family with related structure and function. The Office here is viewing these related peptides in a complete vacuum which wrongly increases the supposed size of the "genus" encompassed by the claim term "isoform." Applicant urges the Office to consider the claimed invention as a whole and to use the broadest reasonable interpretation of the claim term as it would have been understood by a skilled artisan and to keep in mind that "isoform" is not understood by skilled persons to mean any peptide with any degree of similarity. Further, the term "isoform" is not used in isolation, but in a claim with other features as well. Thus, Applicant submits that the structure of isoforms and their function are well understood by artisans.

In discussing chemical properties and functional characteristics, the Office asserts that there is no disclosed correlation between wound healing activity and any structure. Applicant urges the Office to consider the specification as filed, which discusses the amino acid sequence LKKTET (a structure) throughout. The specification makes clear to a skilled reader that peptides, including TB4 and TB4 isoforms, which have this motif or a conservative variant thereof possess wound healing activity. Applicant would like to call the Office's attention in particular to page 9, line 27 to page 10, line 11. This discussion clearly correlates the structure of the claims to the function of the claims. One of skill, reading the specification and claims as a whole would recognize a core structure and common attributes of the wound-healing peptides, contrary to the Office's assertion. A common core sequence is taught in the application here. Therefore, a skilled artisan would not have doubted that the inventors here possessed the claimed invention.

In discussing methods of making the invention, the Office appears to criticize the application for not setting forth examples showing how to make peptides. Applicant submits that skilled artisans know how to make peptides and do not need instruction on what is well known in the art. The Office then again discusses the need to describe a genus with a representative number of species. Applicant has discussed the error in the Office's assumptions both about the size and scope of the "genus" and the specific examples that are disclosed. Applicant submits that the specification as filed has described the invention and has reasonably conveyed to the skilled artisan that the inventors had possession at the time of filing, and that rejection of the claims as inadequately described should be withdrawn.

Claims 136, 173-176 and 186-186 are rejected as not sufficiently described with respect to "lactated Ringer's intravenous polyalkylene glycol," "neuron-degenerative disease," and specific numerical ranges. Disclosure and description of lactated Ringer's intravenous polyalkylene glycol has been discussed above with respect to the international specification. Applicant now refers to the same disclosure in the specification of U.S. serial no. 09/772,445, the present application at page 14, line 29 – page 15, line 1 and page 16, lines 17 and 25.

Applicant has amended the claims to delete the word "about," as discussed above, and repeat the discussion above with respect to the international specification and the numerical ranges of the claims. Applicant submits that the skilled artisan would reasonably believe the inventors possessed the invention as claimed given the description here. Applicant has deleted the claim language relating to "neuron-degenerative disease" and submits that the claims conform to the description requirement of 35 U.S.C. § 112, first paragraph.

Claims 1-3, 5-7, 11, 13-14, 16-18, 22-29, 33-36, 38-39, 53-55, 57-59, 61, 133-136, 173-176 and 183-186 are rejected as anticipated by Mann (U.S. Patent No. 6,030,948). Mann is specifically cited for teaching a composition that contains thymosin factor 5 (TF5), which assertedly contains TB4 and thymosin alpha 1 (TA1), which is

applied to the scalp and therefore is assumed to constitute an acid peel that would result in "abrasion/damage/lesions/wounds" on the skin. The Office therefore appears to be relying on a theory of inherency for the Mann alopecia treatment method.

The Mann method involves six steps, including (4) applying an acid peel solution and (6) applying a hair regeneration composition, which is elsewhere described as potentially including TF5. Nowhere in the Mann patent is there any disclosure whatsoever that indicates the acid peel solution is abrasive or is massaged into the scalp to cause abrasions, or is of such low pH or other character that it is designed to or inevitably causes damage, lesions or wounds to the skin on the scalp. There appears to be nothing in the reference that even hints that the "acid peel" compositions even could create damage, lesions or wounds, much less any disclosure that would lead the reader to assume that the composition necessarily and inevitably, i.e. inherently wounds the scalp.

Persons of skill in the art are aware that the phrase "acid peel" does not refer to any treatment intended to cause any type of wounding to the living skin, but only to cause exfoliation of the outer, dead layer of skin without any damage to the living skin itself. Acid peel certainly does not refer to a treatment that necessarily results in skin wounding. The suggested range of acid in the solutions of Table 10 in Mann discloses very mild solutions that would have been known to the skilled artisan not to damage or wound the skin. In addition, there is nothing to indicate that removal of the acid peel solution would result in wounds. It is commonly known in the art that chemical and acid peel treatments refer to causing the outer dead layers to peel away and not to actually peeling the solution away from the skin in any damaging fashion. Therefore, the Office's conclusion that use of TF5 on the scalp after an acid peel treatment necessarily discloses wound healing is based on a fallacy. Applicant requests reconsideration of this rejection and its withdrawal.

The Office also refers to the ranges of TB4 recited in some dependent claims and requests that Applicant provide the concentration of TB4 in TF5. Applicant refers to Low et al., Proc. Natl. Acad. Sci. USA 78(2):1162-1166, 1981, which indicates that

9.58g TF5 yielded 43.5 mg TB4 (this is about 0.0045 mg TB4 per mg TF5). See Legend to Fig. 1. Mann indicates that its compositions contain 0.01% - 10% TF5 but does not indicate how much of the composition is applied to the scalp.

The Office has considered this evidence and the declaration on this subject previously filed but finds it unpersuasive because the word "wound" in the claims is not defined and is being interpreted to encompass exfoliation of the outer, dead skin layer. Applicant submits that this is not a reasonable interpretation. Nor is it reasonable to interpret "tissue injury" to encompass removal of dead skin cells. Skin which has been exfoliated is not then in need of healing or repair. Applicant urges the Office to consider the invention as disclosed in the specification as a whole and in the context of that disclosure.

Furthermore, the Office States that the claims do not require that the subject have a wound or injury. Claim 1 recites a method for promoting wound healing in a subject in need of such treatment. Applicant submits that such a subject has a wound. The same is true for claims 13 and 23, which relate to wound healing and claim 185, which refers to tissue injury. Applicant submits that an acid peel skin treatment does not cause tissue injury and certainly does not necessarily cause tissue injury. Claim 186 also has been amended to refer to a subject in need thereof and to delete language related to prevention. Therefore, Applicant submits that the declaration of Dr. Fine, filed September 17, 2008, overcomes any rejection of these claims. Applicant requests reconsideration of this evidence and withdrawal of the claims.

The Office considers there to be no showing that the acid peel composition would fail to ulcerate human skin to produce a wound. Applicant submits that it is common knowledge, not only to persons of skill in this art but to ordinary laymen, that the purpose of acid peels is to beautify skin, not to ulcerate it. Although some of the deeper and stronger chemical peel solutions can produce redness and irritation, over-the-counter products often contain acid stronger than the 2.0% citric acid / 1% salicylic acid products which are included in Table 10. Applicant submits that the citric and salicylic acids in Table 10 include extremely mild treatments which do not cause skin

injury. See, for example the attached article from www.articlesbase.com, which discusses types of acid peels. Mann recommends a wide range of peels, including the mildest types of acids, at lower concentrations, and with application times of only one minute. Such peels will not ulcerate the skin and are acceptable for use in over-the-counter, daily use products. See, for example the attached article from www.doctorsecret.com, which describes acid peels of this type, and which states that 10-40% alphahydroxy acid is characterized as "mild." Mann discloses 3-50% and therefore discloses acid peels that are even milder and would not be expected to damage the skin, particularly when used in over-the-counter products designed to be used every day.

Applicant requests reconsideration of the Office's unproven assertion that the Mann method inherently results in wound treatment. The Office bears the burden of proof in this instance and has failed to do so here. Furthermore, Applicant has provided persuasive evidence, in the form of a declaration and otherwise, which show that the inherent disclosure asserted by the Office is not present. Applicant requests withdrawal of the rejection of claims as anticipated by Mann.

Claim 186 is rejected as anticipated by Goldstein et al., (U.S. Patent No. 5,578,570; hereinafter "Goldstein"). As discussed above, this claim has been amended and no longer recites the feature of "prevention." Further, the claim also does not recite "conservative variant" and has been amended for the sake of readability. Applicant submits that this rejection now is moot and requests its withdrawal.

Claims 1-3, 5-8, 11, 13-14, 16-19, 22-29, 33-36, 38-39, 53-55, 57-61, 133-136, 173-176 and 183-186 are rejected as obvious over Mann, discussed above. Mann is cited here for its asserted disclosure of "the use of thymosin beta 4." Mann, however, does not teach or suggest a method for promoting wound healing or treating tissue injury in a subject in need of such treatment with the features of the claims presented here. Mann discloses that TF5, in combination with a number of other active ingredients, re-grows hair. Specification, Mann teaches that the TA1/TB4 (thymic) component of the hair regeneration component "assists in boosting cell-mediated

immunity." Col. 14, lines 44-45. There is no connection made between the wound-healing functions disclosed in the present application, i.e. actin-binding/sequestration, and hair restoration. Therefore, there is no motivation or guidance which would lead the skilled artisan to the method claimed here from the disclosures and fair suggestions of Mann, as they would be understood by a person of skill in the art. Applicant requests reconsideration and withdrawal of this rejection. The Office has not cited any evidence that Mann teaches or suggests all elements of each rejected claim as required.

Because Mann does not teach or fairly suggest the methods of the independent claims here, it also does not render any of the dependent claims obvious. Citation of evidence that Mann mentions TB4 is not sufficient to render obvious a dependent claim when Mann fails to teach or fairly suggest all elements of that claim. Applicant submits that the Office has not made out a prima facie case of obviousness here and has not even attempted to cite evidence of disclosure or suggestion of all claim elements or of any guidance Mann provides to the artisan to achieve what the inventors here claim, with a reasonable expectation of success. Applicant requests the rejection be withdrawn.

Claims 1-2, 5-8, 11, 13, 16-19, 23-28, 33-35, 38-39, 53-55, 57-61, 133-136, 173-176 and 183-186 are rejected as obvious over Malinda et al. (FASEB J.; hereinafter "Malinda"), Baumann et al. (Proc. 2d Int'l Thymus Symp; hereinafter "Baumann") and Biotech Pat. News, 1997 (hereinafter "Alpha 1 Biomedicals"). The Office is citing Malinda as purportedly disclosing that TB4 is useful for wound healing, although it concedes that Malinda does not expressly teach administering TB4 to patients in need of wound healing.

The Office has extrapolated in vitro studies reported in Malinda on human umbilical vein endothelial cells, for example in "scratch" tests, which are termed as "wounds" by the Office, on a cell monolayer to find an asserted motivation to "use the method" in vivo. However, the migration of cells into a scratch on a cell culture plate, which is described in Malinda, does not provide the skilled artisan with any reasonable expectation of success in the far more complex system of an in vivo wound. Although

this cell immigration of endothelial cells "support[s] the idea" that TB4 is involved in angiogenesis (Malinda, page 480, paragraph bridging left and right columns), there is no convincing evidence that it actually does promote angiogenesis. Further, Malinda teaches that TB4 "could play a role in wound healing" (emphasis added). See page 480, right column. This statement does not suggest to the skilled artisan that TB4 should be administered to patients in need of wound healing, particularly in view of the later statement (bridging pages 480-481) that further study would be needed to determine whether stimulation of migration can expedite wound healing in vivo. Therefore, all the disclosures of Malinda with respect to the claimed invention are theoretical at best and provide no reasonable expectation of success for the invention.

The Office refers to Baumann as also supporting its conclusion that the art teaches TB4 heals wounds in vivo. Baumann, however, also does not provide anything more than a guess. These authors list "wound healing" only as an in vitro effect and not as an in vivo effect. Baumann also specifically refers to the speculative nature of their understanding of the function of TB4. As a whole, this reference also does not teach the method claimed here. In combination with Malinda, it adds nothing that would lead the skilled artisan to expect success.

The Alpha 1 Biomedical abstract is a press release or news article rather than a peer-reviewed journal article and therefore should be read in this light as unverified and possibly self-serving. The article reports that an NIH investigator plans to use TB4 "in a wound healing study." The nature of the study or how TB4 is to be used is not disclosed. This is a future or ongoing study, so no results are available. Applicant submits that this news article only suggests that one group of scientists believes that it may be worth trying to use TB4, but exactly how to use it or what exactly to use it for is not even suggested. Since the vast majority of compounds studied do not result in success, the mere announcement that a study is planned does not provide a reasonable expectation of success.

Applicant urges the Office to consider the care with which both of these authors avoid stating the conclusion that the Office makes here in the light of hindsight. In order

to make out a prima facie case of obviousness, the Office has the burden of showing disclosure or suggestion of all claim elements, a reasonable motivation or connection of the disclosures to the claimed invention which guides the artisan to achieve what is claimed, and a reasonable expectation of success, in the absence of hindsight.

In summary, none of the art here provide a reasonable expectation that TB4 would work in the method claimed here. When read as a whole and in combination, from the point of view of a skilled artisan, the art provides no real expectation of success, much less a reasonable expectation of success for the claimed methods. An in vitro "scratch" test does not correlate with success of the claimed invention, as the authors of the cited references, Malinda and Baumann, acknowledge. Applicant requests that the Office withdraw the rejection of these claims as obvious.

Claims 1-8, 11, 13-19, 22-30, 33-36, 38-39, 53-55, 57-61, 133-136, 173-176 and 183-186 are rejected as obvious over the three references discussed immediately above, in further view of Puolakkainen et al. (J. Surg. Res. 85:321-329, 1995; hereinafter "Puolakkainen"). The Malinda, Baumann and Alpha 1 Biomedical references are discussed at length above. Applicant incorporates these remarks here as well, and submits that these references do not provide a reasonable expectation of success for the rejected claims.

Here, the Office also is citing Puolakkainen for disclosing transforming growth factor beta (TGFB) as having beneficial effects on wound healing. This reference does not, however, make up for the failure of the other references to provide a reasonable expectation of success for wound healing as claimed. Further, the Office states that the invention is obvious "in the absence of evidence to the contrary" Office Action, page 30, lines 19-20." However, it is the Office's burden to put forth persuasive evidence of obviousness in the first instance. The Office must make out a prima facie case of obviousness rather than demand Applicants prove nonobviousness.

The Office refers to the terms "isoform" and "conservative variant." Applicant has amended the claims herein and refers the Office to these amendments and to the discussions above with respect to 35 U.S.C. § 112. Applicant also refers the Office to

remarks previously filed and the Fine declaration submitted in a previous response, as well as the discussion above concerning the Fine declaration, and the terms "wound" and "tissue injury."

Applicant submits that Puolakkainen does not make up for the deficiencies of the other three references since it does not even mention TB4 and therefore would not be combined by a person of skill. The combination of the cited references still does not provide a reasonable expectation of success for the claims here. Applicant therefore requests withdrawal of this rejection.

The Office has withdrawn rejections made over claims of U.S. Patent 7,268,118 and U.S. serial nos. 11/284,430 and 10/714,405 and grounds of non-statutory double patenting.

Claims of the present invention are rejected on grounds of non-statutory double patenting over claims 7-16 and 29-47 of serial no. 11/284,408, over claims 13-23 and 26 of serial no. 11/917,869, claims 21-32 of serial no. 11/715,997 and claims 1-25 of serial no. 12/444,331. All of these serial nos. were filed subsequent to the present application. Given that this rejection is a provisional rejection since no conflicting claims have issued or been indicated to be allowed, and because none of the cited references have a prior filing date to the present case, Applicant requests that this rejection be held in abeyance until the present claims are held allowable or until any of the claims of the cited applications have issued and determined to conflict with the claims here, so that the Office can determine whether a terminal disclaimer is warranted in this application. See M.P.E.P. § 804(I)(B)(1).

The sequence listing has been amended to include the sequences of new Table I, which has been added to the specification as discussed above. Figure 11A has been amended to correct an obvious typographical error in the sequence of Tβ4. The sequence of Tβ4 in Figure 11A had originally been depicted as " ... EQEDQ ...." However, the correct sequence of Tβ4 is shown in original Figure 10 ("... EQEKQ ..."). In addition, the Figure 10 sequence was available in the GenBank database prior to the filing date of the present application (see for example accession no. AAA42246.1) and

in the material incorporated from Mihelić. As such, the error and its correction would have been known to one of skill in the art. No new matter is introduced by means of these amendments.

Applicant requests entry of the amendments contained herein, reconsideration of the application and allowance of all claims presented here.

Respectfully submitted,

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